REMARKS

Claims 31-38 were previously pending. Claims 36-38 have been cancelled. Claims 31, 33, 34 and 35 have been amended to replace HIV with HIV-1. Claim 31 has been amended to correct typographical errors. New claim 39 specifies that recombinant MVA virus expresses HIV-1 gp41 "lacking at least 115 amino acids of the cytoplasmic domain of gp41". Support for this amendment is found at paragraph [0144] of the specification. No new matter has been added.

Applicants appreciate the withdrawal of the previous new matter rejections, the withdrawal of several previous indefiniteness rejections and the previous obviousness rejection.

The comments below are based on the Office Action mailed September 13, 2006

Claim objections

Claim 31 has been amended to correct the spelling of "cytoplasmic".

Rejections Under 35 U.S.C. §112, first paragraph (written description)

In the prior office action, the Examiner rejected claims 33-38 as allegedly failing to meet the written description requirement. The Examiner stated that the claims encompass nucleic acids and MVA encoding or expressing variants of gag, pol and env. In particular the Examiner notes that the claims encompass variants of HIV pol having reduced reverse transcriptase activity, reduced strand transfer activity or reduced RNaseH activity. In making this rejection, the Examiner cited *Fiers v. Revel, Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd, Fiddes v. Baird* and *University of California v. Eli Lilly and Co.* Applicants respectfully traverses this rejection.

Claims have been amended to recite HIV-1

Before addressing this rejection in detail, Applicants note that the claims have been amended to refer to " HIV-1" rather than "HIV". The Examiner correctly stated that certain of the examples in the specification are based on HIV HXB2, which is an HIV-1 strain (as opposed

to, for example an HIV-2 strain). The Examiner questioned whether a mutation in one strain, e.g., an HIV-1 strain, would have the same effect in another strain. Given that Applicants have amended the claims to recite HIV-1, Applicants believe that this concern has been addressed.

Legal Standard for Meeting the Written Description Requirement

The USPTO Written Description Requirement Guidelines explain that the written description requirement can be met by a "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Guidelines for Examination of Patent Applications Under 35 U.S.C. 112 Paragraph 1, "Written Description" Requirement.* 66 Fed. Reg. 1099, 1106. In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, the Court of Appeals for the Federal Circuit (CAFC) quoted this portion of the Guidelines with approval stating that "we are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement." 296 F.3d 1261 (Fed. Cir. 2002). Thus, the existence of a known correlation between structure and function is a relevant factor in assessing whether the written description requirement has been met. Accordingly, as discussed in greater detail below, whether a given disclosure meets the written description required for a claimed invention, e.g., a claimed protein or variant protein depends, in part, on the knowledge of those skilled in the art regarding the claimed protein or protein variant.

In two recent cases the CAFC considered the written description requirement in the context of claims drawn to polypeptides (*Invitrogen Corporation v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005); Exhibit A) and in the context of claims drawn to chimeric genes (*Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005); Exhibit B). In both cases the CAFC concluded that the disclosure required to meet the written description requirement depends on the knowledge of those skilled in the art.

In *Invitrogen Corporation v. Clontech Laboratories, Inc.*, 429 F.3d 1052, (Fed. Cir. 2005), the CAFC considered whether the following claim meets the written description requirement.

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNaseH activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in a polypeptide having substantially reduced RNaseH activity and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

Thus, the claim is drawn to a polypeptide encoding a DNA polymerase having reduced RNaseH activity wherein the polypeptide is encoded by a polynucleotide derived from any of a wide range of species as diverse as, for example, primates and retroviruses. The patent disclosed the sequence of a MMLV DNA polymerase deletion mutant lacking RNaseH activity.

In considering this claim the trial court noted that, at the time of the invention, the sequences of several reverse transcriptase gene were known and it was known that several members of the reverse transcriptase gene family shared significant homology. The trial court ultimately concluded the claim recited above meets the written description requirement. This decision was appealed to the CAFC. The appellant, citing *Fiers v. Revel* and *University of California v. Eli Lilly and Co.*, argued that the trial court had erred in finding that the claim meets the written description requirement. The appellant argued that the claim fails to meet the written description requirement because it is not limited to sequences recited in the specification or in the claim. The CAFC upheld the trial court's decision that the claim meets the written description requirement. In doing so, the CAFC stated that the appellant's reliance on *Fiers* and *Eli Lilly* was misplaced because the patent specification at issue in those cases did not disclose the sequence "of any embodiment of the DNA sequence claimed therein." *Invitrogen* at 1073

Thus, it is clear that the disclosure of even <u>one</u> embodiment of a recombinant gene encoding a mutant polypeptide, when coupled with the knowledge of homologous polypeptides in the prior art, can satisfy the written description recruitment for even very broad claims.

In *Capon v. Eshhar*, the CAFC explained that in satisfying the written description requirement, the "descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence". *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005). The claims at issue in *Capon*, which concerned two applications in an interference proceeding, were drawn to chimeric genes comprising a sequence encoding a single-chain variable domain of an antibody and a sequence encoding the cytoplasmic, transmembrane and extracellular domains of a lymphocyte signaling protein. In the proceeding below, the Board of Patent Appeals and Interferences ("BPAI"), citing *Fiers v. Revel, Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd*, and *University of California v. Eli Lilly and Co.*, had held that the claims failed to meet the written description requirement.

> Here [the inventors] claim novel genetic material described in terms of the functional characteristics of the protein it encodes. Their specification do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results.

Both parties in the interference appealed the BPAI's conclusion that the claims failed to meet the written description requirement to the CAFC. The parties argued that they had each provided several examples of the claimed chimeric genes. In addition, both parties presented expert testimony explaining that hundreds of the sequences encoding the various proteins encoded by the claimed chimeric genes were known in the prior art. For example, one party presented evidence that 785 mouse antibody light chain DNA sequences and 1,327 mouse antibody heavy chain DNA sequences were known in the prior art.

The CAFC ruled that the BPAI has erred in holding that there is a *per se* rule requiring recitation in the specification of sequences that are known in the art. In making this ruling, the CAFC distinguished the claims at issue with those in *Fiers v. Revel, Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd*, and *University of California v. Eli Lilly and Co.* stating that in *Fiers* much of the DNA sought to be claimed was "of unknown structure", in *Lilly* the cDNA for

human insulin had never been characterized, and in *Amgen* the court explained that a novel gene was not sufficiently characterized by function alone. The CAFC went on to explain that the written description requirement "states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Capon* at 1356. The CAFC also explained that the description in the specification needed to meet the written description requirement depends on the knowledge in the art.

> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Capon at 1357.

It is clear from the holdings in *Invitrogen* and *Capon* that the law recognizes that the disclosure required to meet the written description requirement depends on the state of the art. In the case of mutant polypeptides and chimeric genes, the CAFC has found that even very broad claims meet the written description requirement where the application itself has few or even only one example, because the prior art itself contains numerous homologs.

The present claims and the knowledge of HIV proteins in the art

The genes and proteins of HIV have been so extensively studied that prior to the priority date of the present invention hundreds of HIV protein and gene sequences from multiple clades and strains were known and were aligned. This information was available in articles, books and databases. Moreover, due to the numerous known variants and mutants of the proteins there was an understood correlation between structure and function for HIV proteins, including HIV pol, as of the priority date of the present application. Indeed, HIV Pol has been particularly intensively studied because it includes the protease and reverse transcriptase functions that are the targets of

the major therapeutic treatments for AIDS. It is Applicants' position that given this knowledge available to those of ordinary skill in the art and given the disclosure of present application, the present claims meet the written description requirement just as the claims at issue in *Invitrogen* and *Capon* were found to meet the written description requirement.

As explained in the previous amendment, the present specification explains that GenBank® and various other sequence databases, such as that found on the internet at http://hiv-web.lanl.gov, provide HIV sequences. As also explained previously, the "HIV Sequences Compendium 2000", Kuiken et al., eds., published by the Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, discloses nearly 100 HIV pol sequences from various clades each of which is aligned with the pol sequence from HIV HXB2 (This is the HIV pol sequence used as the basis for the recombinant MVA described in Example 2 (paragraphs 0136-0154) of the present application). The conserved and variant amino acids are shown and consensus sequences for various clades are presented along with an identification of various functional domains and landmarks within pol, for example, the domains associated with RNaseH activity and integrase activity.[1] This is exactly the type of publicly available information that one can use to identify other HIV pol variants having a mutation that inhibits reverse transcriptase activity, RNaseH activity or strand transfer activity. It is the type of information that the CACF has said applicants are entitled to rely upon. The present claims are far more analogous to the claims considered by the CACF in *Invitrogen v. Clontech* or in *Capon v. Eshhar*. In those cases, as here, numerous homologous genes and polypeptide were known in the prior art. The present situation is <u>not</u> analogous to the factual context of *Fiers v. Revel, Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd*, or *University of California v. Eli Lilly and Co.* where the nucleic acid molecules sought to be claimed were essentially uncharacterized.

---

[1] As also explained previously, numerous mutations within HIV pol that inhibit reverse transcriptase activity, RNaseH activity or strand transfer activity were known to those skilled in the art as of the priority date of the present application. For example, Snyder et al. (*J. Virol.* 74:9668, 2000) describes a mutation at amino acid 478 of HIV pol that interferes with strand transfer activity. Fan et al. (*Biochemistry* 35:9737, 1997) Gao et al. (*J. Mol. Biol.* 277:559, 1998) and Powell et al. (*J. Biol. Chem.* 2772:13262, 1997) describe HIV mutations that reduce RNaseH activity. Finally, Boyer et al. (*Proc. Nat'l Acad. Sci.* 97:3056, 2000) describes mutations that reduce reverse transcriptase activity. These references are just a sampling of the many publications describing mutations that inhibit the activity of HIV pol.

Because a large number of HIV-1 sequences were known in the prior art and because various HIV-1 pol mutations were known in the prior art, Applicants' description of mutations in HIV HXB2 pol that lead to reduced reverse transcriptase activity, reduced strand transfer activity or reduced RNaseH is sufficient to meet the written description requirement of 35 U.S.C. §112, first paragraph for the present claims. In view of this, Applicants respectfully request that the Examiner withdraw this written description rejection under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 31-38 as indefinite. The Examiner said that it is unclear what is meant by the phrase "but lacking all or part of the cytoplasmic domain of gp41". Applicants respectfully traverse this rejection. Claims 36-38 have been cancelled. The rejection of claims 31-35 is traversed.

"If one skilled in the art would understand the bounds of the claim when read in the light of the specification, then the claim satisfies section 112, paragraph 2." *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Because the sequence and domain structure of gp41 were well known as of the priority date of the application and because the application provides a working example of a HIV env gene encoding "the membrane-spanning domain and ectodomain but lacking all or part of the cytoplasmic domain of gp41", one skilled in the art would understand the meaning of the phrase "but lacking all or part of the cytoplasmic domain of gp41".

First, as of the priority date of the present application, those skilled in the art understood the domain structure of gp41. For example, Salzwedel et al. (*Journal of Virology* 73:2469, 1999; Exhibit C) described mutations in the cytoplasmic domain of gp41 and showed the precise location of the domain and the mutation within the domain. Even earlier, Freed et al. (*Journal of Virology* 70:341, 1996; Exhibit D) described mutations of the cytoplasmic of gp41 and the effect of the deletions on envelope incorporation into virions. In fact, more than 10 years before the priority date of the present application, Gallaher et al (*AIDS Research and Human Retroviruses* 5:431, 1989; Exhibit E) proposed a domain structure for gp41 based on the known

structure of influenza transmembrane protein. Is clear that those skilled in the art have long known what is meant by the term "cytoplasmic domain of gp41". Thus, the phrase is clear, not indefinite. The phrase "all or part" is definite as well.

Second, the present specification, at Figure 15F, provides the sequence of a gene encoding a truncated ADA env, and the specification provides an example of a gp41 lacking 115 amino acids of the gp41 cytoplasmic domain (see paragraph [0144]) .

Thus, it is Applicants' position that those of ordinary skill in the art would understand the meaning of the phrase "lacking all or part of the cytoplasmic domain of gp41". In view of this, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 31-35 as obvious in view of Kent et al. (*J. Virol.* 72:10181, 1998; "Kent") taken with Small et al. (U.S. Patent No. 5,676,950; "Small") and Gao et al. (*J. Mol. Biol.* 277:558, 1998; "Gao"). According to the Examiner, Kent discloses "methods of inducing CTL responses to HIV antigens utilizing methods consisting of priming with DNA and boosting with recombinant Fowlpox" expressing "the *gag*, *pol*, and *env* genes of HIV-1." The Examiner concluded that Kent "differs from the instant invention in that they don't disclose the use of a recombinant MVA virus." The Examiner stated that Small discloses the use of MVA viruses to immunize animals and teaches that MVA is "a safe version of recombinant pox virus". The Examiner stated that Gao discloses plasmids encoding HIV-1 IIIB pol having mutations that inhibit reverse transcriptase activity, strand transfer activity and RNaseH activity." Finally, the Examiner concluded that it would have been obvious to use the MVA of Small in the method of Kent while incorporating the mutations described by Gao in order to take advantage of the safety afforded by MVA vectors and non-functional pol.

Applicants respectfully traverse this rejection for at least the reason that the cited references simply do not teach the elements of the presently claimed invention. The MVA

employed in the presently claimed methods expresses: "HIV Gag, HIV Pol lacking the integrase domain, HIV gp120 and HIV gp41, lacking all or part of its cytoplamic domain."

Kent does not teach a fowlpox virus expressing HIV-1 gag, env and pol

Kent describes two different recombinant fowlpox virus. One recombinant fowlpox virus expresses HIV-1 gag, HIV-1 pro and HIV-1 pol. The other recombinant poxvirus expresses HIV-1 env. Both of these recombinant fowlpox viruses are described on page 10181 in the second paragraph under the heading "Recombinant Poxvirus". Thus, as Applicants previously explained, none of the recombinant poxvirus used by Kent expressed HIV gag, HIV pol and any portion of HIV env. For this reason alone, the cited references, no matter how combined cannot render the present claims obvious.

If the Examiner continues to assert that Kent teaches a recombinant fowlpox virus that expresses HIV-1 gag, HIV-1 env and HIV-1 pol, Applicants respectfully request that the Examiner quote the passage in Kent that the Examiner is relying on for this teaching.

Kent does not teach a fowlpox virus expressing HIV-1 pol lacking the integrase domain

The MVA employed in the presently claimed methods express an HIV-1 pol lacking the integrase domain. As explained previously, the recombinant fowlpox used by Kent apparently expressed intact HIV pol. There is no evidence in Kent that the HIV pol expressed by the recombinant Fowlpox lacks the integrase domain, as required by the present claims. For this reason alone, the cited references, no matter how combined cannot render the present claims obvious. In the present action, the Examiner did not note where in Kent or where in the other cited references the Examiner finds a teaching or suggestion to express an HIV-1 pol lacking the integrase domain. If the Examiner maintains the present obviousness rejection, Applicants respectfully request that the Examiner identify the passage in the cited references that the Examiner relies on for teaching a recombinant virus expressing HIV-1 pol lacking the integrase domain.

Kent does not teach use of a fowlpox virus expressing an HIV-1 lacking all or part of the cytoplasmic domain of gp41

The MVA employed in the presently claimed methods express an HIV-1 gp41 lacking all or part of the cytoplasmic domain. As explained in Applicants' previous amendment, the recombinant fowlpox used by Kent apparently expressed intact HIV-1 env, i.e., env having an intact gp120 and an intact gp41. There is no evidence in Kent that the HIV-1 gp41 expressed by the recombinant Fowlpox lacks all or part of the cytoplasmic domain, as required by the present claims. For this reason alone, the cited references, no matter how combined cannot render the present claims obvious. In the present action the Examiner did not note where in Kent or where in the other cited references the Examiner finds a teaching or suggestion to express an HIV-1 gp41 lacking all or part of the cytoplasmic domain. If the Examiner maintains the present obviousness rejection, Applicants respectfully request that the Examiner identify the passage in the cited references that the Examiner relies on for teaching a recombinant virus expressing HIV-1 gp41 lacking all or part of the cytoplasmic domain.

The cited references do not teach or suggest the presently claimed methods

As detailed above, the Examiner is simply incorrect in stating that Kent "differs from the instant invention in that they don't disclose the use of a recombinant MVA virus." In truth, Kent differs from the presently claimed invention in several ways. Small and Gao do not teach or suggest the use of HIV-1 pol lacking the integrase domain or the use of HIV-1 gp41 lacking all or part of the cytoplasmic domain. Thus, the cited references, no matter how combined, do not teach or suggest the presently claimed invention.

In view of the forgoing, Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 4 APRIL 2007

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906